

REMARKS

I. Preliminary Comments and Amendments to the Specification

Claims 1-27 were subject to a restriction requirement. Applicants selected Group II, claims 6-12, without traverse. With the August 22, 2005 Office Action, the restriction requirement is made final.

Applicants have amended the specification to correct an obvious typographical error which was recently discovered. This typographical error relates to the summary sequence listing of the ENTH domain as it appears in the specification on page 2, lines 29-31. Specifically, the summary sequence provided at page 2 is inconsistent with the sequences provided for the ENTH domains in each of SEQ ID NOs 1, 2, 3, 4, and 5 as well as the consensus ENTH domain sequence presented in Fig. 1 of Kay et al. (*Protein Sci.* 8(2): 435-8 (1999)), which was cited by applicants at page 6, lines 33-34 and page 39, lines 28-31 of their specification and is attached hereto as Appendix 2 to the Declaration of Barbara Froesch Ph.D. The page 2 sequence is also inconsistent with the ENTH domain of Epsin protein sequences presented in FIG 1A of Rosenthal et al. (*J Biol Chem*, 274(48): 33959-33964 (1999)), which was cited by applicants at page 6, line 35 and page 41, line 13 of their specification and is attached hereto as Appendix 3 to the Declaration of Barbara Froesch Ph.D. This inconsistency is clearly seen in the following sequence alignments, where the number in parentheses is the number of the amino acid residue that begins the ENTH domain in each sequence:

ENTH Domain (as filed)

N- X (11-13) -V- X2-A-T- X (34-36) -

ENTH Domain (as corrected)

N- X (11-13) -V- X2-A-T- X (34-36) -

SEQ ID No 1

(16)N-V-V-M-N-Y-S-E-I-E-S-K-V-R-E-A-T-N-D-D-P-W-G-P-S-G-Q-L-M-G-E-I-A-K-A-T-F-M-Y-

SEQ ID No 2

(16)N-V-V-M-N-Y-S-E-I-E-S-K-V-R-E-A-T-N-D-D-P-W-G-P-S-G-Q-L-M-G-E-I-A-K-A-T-F-M-Y-

SEQ ID No 3

(20)N-V-V-M-N-Y-T-E-T-E-G-K-V-R-E-A-T-N-D-D-P-W-G-P-T-G-P-L-M-Q-E-L-A-Y-S-T-F-S-Y-

SEQ ID No 4

(20)N-V-V-M-N-Y-T-E-T-E-G-K-V-R-E-A-T-N-D-D-P-W-G-P-T-G-P-L-M-Q-E-L-A-Y-S-T-F-S-Y-

SEQ ID No 5

(16)N-V-V-M-N-Y-S-E-I-E-S-K-V-R-E-A-T-N-D-D-P-W-G-P-S-G-Q-L-M-G-E-I-A-K-A-T-F-M-Y-

Rosenthal et al. FIG 1A rEPSIN2a

(12)N-I-V-N-N-Y-S-E-A-E-I-K-V-R-E-A-T-S-N-D-P-W-G-P-S-S-L-M-T-E-I-A-D-L-T-Y-N-V-

Rosenthal et al. FIG 1A rEPSIN2

(12)N-I-V-N-N-Y-S-E-A-E-I-K-V-R-E-A-T-S-N-D-P-W-G-P-S-S-L-M-T-E-I-A-D-L-T-Y-N-V-

Rosenthal et al. FIG 1A rEPSIN1

(12)N-I-V-H-N-Y-S-E-A-E-I-K-V-R-E-A-T-S-N-D-P-W-G-P-S-S-L-M-S-E-I-A-D-L-T-Y-N-V-

Kay et al. FIG 1 consensus sequence

N- X (11-13) -V- X2-A-T- X (34-36) -

ENTH Domain (as filed)

-R- X (7-8) -W-R- X3 -K- X12

ENTH Domain (as corrected)

-R- X (7-8) -W-R- X3 -K- X11

SEQ ID No 1

-E-Q-F-P-E-L-M-N-M-L-W-S-R-M-L-K-D-N-K-K-N-W-R-R-V-Y-K-S-L-L-L-A-Y-L-I-R-N-

SEQ ID No 2

-E-Q-F-P-E-L-M-N-M-L-W-S-R-M-L-K-D-N-K-K-N-W-R-R-V-Y-K-S-L-L-L-A-W-L-I-R-N-

SEQ ID No 3

-E-T-F-P-E-V-M-S-M-L-W-K-R-M-L-Q-D-N-K-T-N-W-R-R-T-Y-K-S-L-L-L-L-N-Y-L-V-R-N-

SEQ ID No 4

-E-T-F-P-E-V-M-S-M-L-W-K-R-M-L-Q-D-N-K-T-N-W-R-R-T-Y-K-S-L-L-L-L-N-Y-L-V-R-N-

SEQ ID No 5

-E-Q-F-P-E-L-M-N-M-L-W-S-R-M-L-K-D-N-K-K-N-W-R-R-V-Y-K-S-L-L-L-L-A-Y-L-I-R-N-

Rosenthal et al. FIG 1A rEPSIN2a

-V-A-F-S-E-I-M-S-M-V-W-K-R-L-N-D-H-G-K-N- W-R-H-V-Y-K-A-L-T-L-L-D-Y-L-I-K-T-

Rosenthal et al. FIG 1A rEPSIN2

-V-A-F-S-E-I-M-S-M-V-W-K-R-L-N-D-H-G-K-N- W-R-H-V-Y-K-A-L-T-L-L-D-Y-L-I-K-T-

Rosenthal et al. FIG 1A rEPSIN1

-V-A-F-S-E-I-M-S-M-I-W-K-R-L-N-D-H-G-K-N- W-R-H-V-Y-K-A-M-T-L-M-E-Y-L-I-K-T-

Kay et al. FIG 1 consensus sequence

-R- X (7-8) -W-R- X3 -K- X11

ENTH Domain (as filed)ENTH Domain (as corrected)SEQ ID No 1SEQ ID No 2SEQ ID No 3SEQ ID No 4SEQ ID No 5Rosenthal et al. FIG 1A rEPSIN2aRosenthal et al. FIG 1A rEPSIN2Rosenthal et al. FIG 1A rEPSIN1Kay et al. FIG 1 consensus sequence

-G-X-E-	X15	-L-	X(11-12)-	D-X-G-(null)R-
-G-X-E-	X15	-L-	X(10-11)-	D-X-G- X3 -R-
-G-S-E-R-V-V-T-S-A-R-E-H-I-Y-D-L-R-S-L-E-N-Y-H-F-V-D-E-H-G-K-D-Q-G-I-N-I-R-Q-K-				
-G-S-E-R-V-V-T-S-A-R-E-H-I-Y-D-L-R-S-L-E-N-Y-H-F-V-D-E-H-G-K-D-Q-G-I-N-I-R-Q-K-				
-G-S-E-R-V-V-T-S-S-R-E-H-I-Y-D-L-R-S-L-E-N-Y-T-F-T-D-E-G-G-K-D-Q-G-I-N-V-R-H-K-				
-G-S-E-R-V-V-T-S-S-R-E-H-I-Y-D-L-R-S-L-E-N-Y-T-F-T-D-E-G-G-K-D-Q-G-I-N-V-R-H-K-				
-G-S-E-R-V-V-T-S-A-R-E-H-I-Y-D-L-R-S-L-E-N-Y-H-F-V-D-E-H-G-K-D-Q-G-I-N-I-R-Q-K-				
-G-S-E-R-V-A-Q-D-C-R-E-N-I-F-A-I-Q-T-L-K-D-F-Q-Y-I-D-R-D-G-K-D-Q-G-I-N-V-R-E-K-				
-G-S-E-R-V-A-Q-D-C-R-E-N-I-F-A-I-Q-T-L-K-D-F-Q-Y-I-D-R-D-G-K-D-Q-G-I-N-V-R-E-K-				
-G-S-E-R-V-S-Q-D-C-K-E-N-M-Y-A-V-Q-T-L-K-D-F-Q-Y-V-D-R-D-G-K-D-Q-G-V-N-V-R-E-K-				
-G-X-E-	X15	-L-	X(10-11)-	D-X-G- X3 -R-

ENTH Domain (as filed)ENTH Domain (as corrected)SEQ ID No 1SEQ ID No 2SEQ ID No 3SEQ ID No 4SEQ ID No 5Rosenthal et al. FIG 1A rEPSIN2aRosenthal et al. FIG 1A rEPSIN2Rosenthal et al. FIG 1A rEPSIN1Kay et al. FIG 1 consensus sequence

X11-	D-	X7	-R-
X11-	D-	X7	-R-
-V-K-E-L-V-E-F-A-Q-D-D-D-R-L-R-E-E-R-			
-V-K-E-L-V-E-F-A-Q-D-D-D-R-L-R-E-E-R-			
-V-R-E-L-I-D-F-I-Q-D-D-D-R-L-R-E-E-R-			
-V-R-E-L-I-D-F-I-Q-D-D-D-R-L-R-E-E-R-			
-V-K-E-L-V-E-F-A-Q-D-D-D-R-L-R-E-E-R-			
-S-K-D-L-V-A-L-L-K-D-E-E-R-L-K-A-E-R-			
-S-K-D-L-V-A-L-L-K-D-E-E-R-L-K-V-E-R-			
-A-K-D-L-V-A-L-L-R-D-E-D-R-L-R-E-E-R-			
X11-	D-	X7	-R-

The Kay et al. reference was cited by the applicants at page 6, lines 33-34 and at page 39, lines 28-31 (Kay et al. *Protein Sci.* 8(2): 435-8 (1999)) (attached as Appendix 2 to the declaration of Exhibit A). It is observed that the summaries of the ENTH domain sequence provided in the Kay abstract, and at Kay, page 436, column 1, lines 3-4 and page 437, column 1, lines 2-3 contain the same typographical error as was made in the specification on page 2 of the present application. Nevertheless, those of ordinary skill in the art would have referred to the Figure 1 alignment of the primary structures of the ENTH domain of 11 proteins in Kay (Appendix 2, Fig. 1) which shows the correct summary sequence for the ENTH domain. This error and its correction would thus have been obvious to one of ordinary skill in the art.

A Declaration by Barbara Froesch Ph.D is attached as Exhibit A to this Response, attesting that a person of skill in the art would have recognized that the summary sequence listing as represented on page 2, lines 29-31 of the specification and the sequences of SEQ. ID NOs 1, 2, 3, 4, and 5 were inconsistent, and that the person of skill in the art would have then looked to the cited Kay and Rosenthal references for guidance in resolving this conflict. The person of skill in the art would have further recognized that the same typographical error for the summary sequence occurred in the text of the Kay reference. Moreover, the person of ordinary skill in the art would have recognized that the correct summary sequence for the ENTH domain is the one derived from the primary structure alignment of Figure 1 of the Kay reference. Thus, no new matter is being introduced with this amendment to the specification.

Claims 6 and 9 are amended in this response to incorporate language suggested by the Patent Office and clarify the language of the claims. No new matter is introduced with these amendments to the claims.

II. Subject Matter of the Invention

The present application relates to the discovery that the ELP protein is a tumor suppressor (see page 6, lines 3-30, and Example X, page 35, lines 1-30), and that alterations in expression levels of ELP, mutations in the nucleic acid sequence encoding an ELP protein, or rearrangements in the genomic *elp* locus correlate with altered tumor suppressor activity and, consequently, with hyperproliferative diseases or a predisposition thereof. (See page 9, line 31 – page 11, line 9). In addition, Applicants have provided methods of analyzing samples of subjects to identify abnormalities in ELP, either in protein or mRNA expression

or in mutations of the DNA sequence, as a means of identifying a hyperproliferative disease.
(See Example XI, page 35, line 33 – page 36, line 22).

III. Outstanding Rejections

Claims 6-12 stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement.

Claims 6-12 stand further rejected for indefiniteness under 35 U.S.C. §112, second paragraph.

Claim 9 stands objected to for having an improper antecedent basis.

IV. Patentability Arguments

A. Objection to Claim 9

The objection to claim 9 for improper antecedent basis can be withdrawn in light of the amendment to claim 9, incorporating the limitations of claim 2. No new matter was introduced with this amendment, and it is submitted that this objection can properly be withdrawn.

B. Rejection of Claims 6-12 under 35 U.S.C. §112, First Paragraph

The lack of enablement rejection of claims 6-12 under 35 U.S.C. §112, first paragraph should be withdrawn because Applicants have shown a nexus between the identification of a hyperproliferative disease and a) changes in the expression level of an ELP protein, b) mutations in a nucleic acid sequence encoding an ELP protein, and c) rearrangements in the genomic *elp* locus.

The ELP protein has been shown to be a tumor suppressor in the present application, whereby changes in its expression level or DNA sequence can indicate a hyperproliferative disease or predisposition thereof. The present application enables one of skill in the art to analyze genetic material of patients or subjects to identify abnormalities, and provides different diagnostic methods (page 10, line 25 – page 11, line 9), and further as applied to ELP protein of SEQ ID NO.: 1 (page 11, lines 10-28). Further guidance is given in Example

XI (page 35, line 33 – page 36, line 22), which shows a cancer profiling array approach, where dot blot hybridization using a specific help probe under specific hybridization conditions shows different expression levels in probes derived from different cancer patients. Such a method can easily be used with any human RNA or cDNA samples to detect changes in expression level (either up or down regulation, see page 36, Table 3).

The lack of enablement rejections should be withdrawn because, first, Applicants have enabled the claimed methods by providing relevant working examples and guidance to those of skill in the art following their claimed methods. Second, Applicants' studies of ELP with *Drosophila* models are both relevant to and applicable to humans. And lastly, while growth factors may have vastly different effects, ELP is not a growth factor but a tumor suppressor, which has been shown to have comparable effects within this class of genes.

1. Applicants Presented Relevant Working Examples

The Patent Office's argument that the Applicants have furnished neither working nor prophetic examples to practice the claimed methods is based upon an incomplete reading of the disclosure and the state of the art and is incorrect. While the examples supplied in the specification measure mRNA expression of hELP, not ELP protein expression levels, it was recognized at the time of filing that a correlation exists between altered levels of RNA and altered levels of protein.

The contention that mRNA levels are not necessarily correlated to protein levels is incorrect because it relies on conclusions proposed in Haynes et al., *Electrophoresis* 19: 1862-1871 (1998), while a later publication by the same authors, which studied a wide range of genes, (Gygi et al., *Mol. Cell Biol.* 19: 1720-1730 (1999); Exhibit B), concluded that "[f]or the entire group [of 106 genes] for which the complete data set was generated, there was a general trend of increased protein levels resulting from increased mRNA levels." (Exhibit B, p 1726) This later study distinguished genes of low (e.g., less than 10 copies/cell) message level and abundant message level, indicating that this correlation was true only for abundant message level proteins.

In a later paper (Gygi et al., *Proc. Natl. Acad. Sci. USA* 97: 9390-9395 (2000); Exhibit C), the same authors concluded that two dimensional gel electrophoresis coupled with mass

spectrometry (2D-MS) - the analytical method used in the publication cited by the Patent Office - is *not* an effective means of analyzing proteins of medium to low abundance. (Exhibit C, p 9390) This is significant because the majority of genes analyzed in the reference cited by the Patent Office *were* low abundance genes. (*see* Haynes et al., 1998, Figure 1) Therefore, the conclusions of the Haynes reference cited by the Patent Office are not relevant to the present invention.

In an independent study by a different group (Futcher et al., *Mol. Cell. Biol.* 19: 7357-7368 (1999), Exhibit D), the authors demonstrated a *strong* correlation between RNA and protein levels using 2D-MS. (Exhibit D, p 7360) Thus, it was recognized at the time of filing of the present application that a correlation exists between altered levels of RNA and altered levels of protein, and the examples in the present application measuring levels of RNA are enabling for the presently claimed method.

2. Drosophila Studies Are Relevant to Human ELP

Applicants have shown that *Drosophila elp* studies are applicable to humans via the rescue experiment of Example III (page 23, line 17 – page 26, line 5). The ability to rescue a *Drosophila elp* mutant with a human copy of the gene would occur only if the human gene was a true human functional homolog. Moreover, *Drosophila* has been shown to be highly suitable for studying tumor suppressor genes, and *elp* is a tumor suppressor gene (page 6, lines 27-30; page 7, lines 22-36; and Example III).

Drosophila has proven to be especially suitable to study cellular mechanisms in carcinogenesis not only due to its accessibility for genetic studies but also due to the high conservation between human and *Drosophila* genes and their function. (Potter et al., *Trends Genet* 16: 33-39 (2000); Exhibit E). It is acceptable to apply *Drosophila* studies to human genes when the genes involved are conserved a) on the basis of nucleotide or amino acid sequence and b) on their phenotype when mutated. For example, *Drosophila* mutants for the gene *gigas*, the fly homolog of the human tumor suppressor involved in tuberous sclerosis complex (TSC), not only show overgrowth but also show tumors of giant polyploid cells, which are a phenotype resembling the human tuberous sclerosis tumors. (*See* Ito and Rubin, *Cell* 96: 529-539 (1999); Exhibit F). The functions of other well known tumor suppressors like APC, LATS, PTEN, and Patched have also been studied in *Drosophila* (*see* Exhibit E).

Therefore, it is legitimate to study cellular processes regulating growth in *Drosophila* and transfer those results into humans where the genes involved, because both the nucleic acid sequence and the phenotype are homologous.

Applicants have shown that the human ELP gene is homologous to *Drosophila* via rescue experiments using human homologs of the *Drosophila* gene. (See Example III, page 23, line 17 – page 26, line 5). Rescue experiments have long been accepted in the art as a valid means through which to verify homology. *Drosophila* homozygous mutants would die during development or have deficits as adults, unless they are “rescued.” Rescued flies survive development and show no phenotype. Rescuing occurs when a normal, non-mutated, copy of the mutated *Drosophila* gene is brought back by genetic engineering as a transgene into the homozygous mutant *Drosophila*. A human gene having a similar sequence is not sufficient to replace a *Drosophila* gene; rather, there must be functional similarity between the human and *Drosophila* genes for successful rescue experiments. (See von Mering and Basler, *Curr Biol* 9:1319-1322 (1999); Exhibit G, p 1322 and Figure 3) Consequently, a person skilled in the art should expect a mutated *Drosophila* to be rescued by a human copy of the gene, if the human gene is a true human functional homolog of the corresponding *Drosophila* gene. The present application contains rescue experiments that show the human ELP gene is capable of rescuing *Drosophila elp* mutant flies (see page 25, Table 1). Therefore, it is legitimate to conclude that the function of the human ELP protein must be the same as the function of the *Drosophila* ELP protein, and studies performed with *Drosophila* can be applied to humans.

Applicants have shown that the ELP protein is a tumor suppressor. If genes are altered during carcinogenesis in a way that leads to a loss of their function, those genes are considered as tumor suppressors. (Robertson et al., *Mol Cell Biol Res Commun* 2: 1-10 (1999); Exhibit H). In order to mimic the effect of a potential tumor suppressor so as to study its role in carcinogenesis, its activity must be decreased or even removed from the model system. To do this, specific recombination sites (FRT sites) are introduced into the chromosomes of *Drosophila*. Deliberately inducing expression of a flipase enzyme, which catalyzes recombination between the FRT sites of the chromosomes, causes a dividing cell to split into two genetically different sister cells. The correct placement of the recombination sites with respect to the heterozygous mutation generates a homozygous mutant and a

homozygous wild-type sister cell from a heterozygous mutant background. The flipase is brought under the control of a heat-inducible promoter, so that the application of a heat shock during late developmental stages generates homozygous mutant cells late in development. Such methods were state of the art in the *Drosophila* field at the time of the present application's filing date and have not only been crucial to study single genes but also to screen the entire genome for new genes. (Golic, *Science* 252: 958-961 (1991); Exhibit I) Incorporation of an eye-specific flipase, ey-flp, has been used to screen for genes that affect growth. Ey-flp, when combined with FRT sites, resulted in recombination events in the developing eye only, whereas the remaining part of the body was not affected at all. (Oldman et al., *Genes Dev* 14: 2689-2694 (2000); Exhibit J) Several research groups successfully applied this pinhead/bighead-screening method to identify tumor suppressors and oncogenes: Tsc1 (Tapon et al., *Cell* 105: 345-355 (2001); Exhibit K); Shar-pei/Salvador (Kango-Singh et al., *Development* 129: 5719-5730 (2002); Exhibit L; and Tapon et al., *Cell* 110: 467-478 (2002); Exhibit M); Hippo (Udan et al., *Nat Cell Biol* 5: 914-920 (2003); Exhibit N); TOR (Exhibit J); and Rheb (Stocker et al., *Nat Cell Biol* 5: 559-565 (2003); Exhibit O).

The method applied in the invention to identify the Elp gene, i.e. the pinhead/bighead screen, was a state of the art method and had already been validated for the identification of tumor suppressor genes and oncogenes. For the person skilled in the art, the ELP protein is considered as tumor suppressor not only because of the method by which it was found, but also and in particular by the effect it exhibited when this method was applied, i.e. the complementation experiment of Example III of the present application (p. 23, line 34 – p. 26, line 5, Table 1 and Figure 6).

3. The ELP Protein Is a Tumor Suppressor and the Examples of Unpredictable Biological Activity of Various Growth Factors Are Not Relevant to ELP

The Patent Office's contention that members of the same gene family can have distinct, and sometimes opposite, biological activities, while true for the examples given in the Office Action (PDGF, VEGF, TGF, OP-1, BMP-2, TGF- β -1, PTH, and PTHrP), is not true for all genes, and is not relevant to the *elp* gene because the examples given in the Office Action are growth factors. Growth factors are usually small, extracellular proteins with hormonal function, i.e. they are signals for other, often very distant, cells. Numerous

members of each growth factor family, e.g., at least 42 members of the TGF-family, have been identified. Growth factors do *not* possess an enzymatic function, but work by binding to receptors, i.e. they act as ligands. There are also numerous receptors in every family, and the ligands bind to various receptors with different affinities. Thus, in theory, every ligand-receptor combination can elicit a distinct and even opposite activity. It is therefore very likely that small changes in the amino acid sequence of the growth factors can change their receptor-preference and, therefore, the activity of the growth factor.

In contrast, though, the protein described in the current application, and further examples given in the specification (TOR, MYC, RAS, PTEN, LATS and TS1, p. 6, lines 22-24) are tumor suppressors, not growth factors. Even though they affect growth, they are not extracellular ligands, but membranous or intracellular proteins. The ELP protein is an intracellular protein and cannot, therefore, be considered a growth factor. While it is possible that other proteins with similar amino acid sequence have distinct if not opposite activity to the ELP protein, such proteins would fail in the above described rescue experiments and would not fulfill the requirement of being a true functional homolog of the growth repressing protein described in the current application. Additionally, the gene expression data presented in the current patent application strongly suggest that tumor cells do have an advantage in down-regulating hELP (Figure 5 and Table 3). Most of the tumor samples presented (page 36, Table 3) display reduced hELP mRNA levels compared with the adjacent normal tissue, thereby favoring a growth repressing role for hELP, and strongly arguing against an opposite (growth promoting) effect. For these reasons, the disclosed human ELP gene would display a growth inhibiting function like its *Drosophila* homolog.

In view of the above arguments and supplied references, it is submitted that Applicants have enabled the claimed method, and that no undue experimentation would be required for one of skill in the art to practice the claimed methods. Therefore, rejection of claims 6-12 under 35 U.S.C. § 112, first paragraph, should be withdrawn.

C. Rejection of Claims under 35 U.S.C. §112, Second Paragraph

The rejection of claims 6-12 under 35 U.S.C. §112, second paragraph for being incomplete may be withdrawn in view of the amendment to claim 6 which adds both a selection step and a conclusion step to the claimed method. Specifically, Applicants have

amended claim 6 as suggested by the Patent Office to recite that the detection is done on a sample of a subject in need thereof, and have further amended claim 6 to include a conclusion step of correlating the detected change to the occurrence of a hyperproliferative disease. Support for this amendment can be found in Example XI, page 35, line 33 – page 36, line 22. Claim 6 is also amended to delete the phrase “in particular benign and malignant tumors, or a genetic predisposition thereof.”

In view of these amendments, the rejections of claims 6-12 under 35 U.S.C. § 112, second paragraph, should be withdrawn.

V. Conclusion

In view of the above amendment and remarks, applicants believe the pending application is in condition for allowance. Should the Examiner wish to discuss any issues of form or substance in order to expedite allowance of the pending application, he is invited to contact the undersigned attorney at the number indicated below.

Dated: December 19, 2005

Respectfully submitted,

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EXHIBIT LIST

Exhibit A – Declaration of Barbara Froesch Ph.D. regarding amendment to the Specification

Appendix 1 – CV of Barbara Froesch Ph.D.

Appendix 2 – Kay, et al., *Protein Sci.* 8: 435-438 (1999)

Appendix 3 – Rosenthal et al., *J Biol Chem* 274(48): 33959-33964 (1999)

Exhibit B – Giyi et al., *Mol Cell Biol* 19: 1720-1730 (1999)

Exhibit C – Gygi et al., *Proc. Natl. Acad. Sci. USA* 97: 9390-9395 (2000)

Exhibit D – Futcher et al., *Mol. Cell. Biol.* 19: 7357-7368 (1999)

Exhibit E – Potter et al., *Trends Genet* 16: 33-39 (2000)

Exhibit F – Ito and Rubin, *Cell* 96: 529-539 (1999)

Exhibit G – von Mering and Basler, *Curr Biol* 9:1319-1322 (1999)

Exhibit H – Robertson et al., *Mol Cell Biol Res Commun* 2: 1-10 (1999)

Exhibit I – Golic, *Science* 252: 958-961 (1991)

Exhibit J – Oldham et al., *Genes Dev* 14: 2689-2694 (2000)

Exhibit K – Tapon et al., *Cell* 105: 345-355 (2001)

Exhibit L – Kango-Singh et al., *Development* 129: 5719-5730 (2002)

Exhibit M – Tapon et al., *Cell* 110: 467-478 (2002)

Exhibit N – Udan et al., *Nat Cell Biol* 5: 914-920 (2003)

Exhibit O – Stocker et al., *Nat Cell Biol* 5: 559-565 (2003)